REMARKS/ARUGMENTS

Upon entry of this amendment, claims 1-12 will be canceled without prejudice or disclaimer, and claims 13-25 will be added, whereby claims 13-25 will be pending. Claims 13, 15, 17-19, 20, 22 and 24 are independent claims.

The claims are amended herein in accordance with the Examiner's suggestion that the claims be written in method format instead of compound/composition format. Moreover, the claims have been cosmetically amended to remove "the step of" terminology, and to recite human in dependent claims.

Still further, Applicants note that amendments have been made to the specification.

Reconsideration and allowance of the application are respectfully requested.

Discussion Of July 3, 2003 Interview

Applicants express appreciation for the courtesies extended by the Examiner to attorney Arnold Turk during a July 3, 2003 personal interview at the Patent and Trademark Office.

During the interview, the disclosed and claimed subject matter was thoroughly discussed. Proposed amendments to the claims to modify the claims to recite methods were discussed, and amendments in conformance with such discussion are included herein. Moreover, the prior art utilized in the rejections was discussed with it being pointed at that Muller is discussed and contrasted in Applicants' specification. The Examiner asserted that compounds disclosed in Muller have a similar function and activity as thioredoxin, and indicated that arguments should be presented with respect to this assertion.

Submission Of Supplemental Information Disclosure Statement

Applicants are filing on even date herewith a Supplemental Information Disclosure Statement. The Examiner is respectfully requested to indicate consideration of this supplemental disclosure statement by initialing the Form PTO-1449 submitted therewith, and forwarding an initialed copy of the form with the next communication from the Patent and Trademark Office.

Response to Formal Matters

Applicants express appreciation for the inclusion with the Office Action of a copy of the initialed Form PTO-1449, whereby the Examiner's consideration of the Information Disclosure Statement filed January 29, 2002 (not January 28, 2002 as indicated by the Examiner) is of record.

Applicants also express appreciation for the acknowledgment in the Office Action of the claim of foreign priority as well as receipt all copies of the certified copies of the priority documents in this national stage application.

Applicants note that the drawings submitted with the application have been accepted.

Response To Prior Art Rejections

The following rejections are set forth in the Official Action:

(a) Claims 1-3 are rejected under 35 U.S.C. 102(b) as being anticipated by Arteel et al. (hereinafter "Arteel"), Chem. Res. Toxic. 1999. In this ground of rejection, the Examiner asserts that the claimed compounds are disclosed by Arteel.

(b) Claims 4-11 are rejected under 35 U.S.C. 103(a) as being unpatentable over the

combined teachings of Arteel and Muller et al. (hereinafter "Muller"), Biochemical Pharmacology, 1984. In this ground of rejection, the Examiner notes that Arteel is different by noting that Arteel does not teach that the same substrate is also an enhancer of the peroxidase activity of thioredoxin reductase. However, the Examiner asserts that Muller teaches that Ebselen (Applicants' disclosed Compound A) is an enhancer of peroxidase activity. From this, the Examiner contends that it would have been obvious to use the substrate of the thioredoxin reductase of Arteel for the enhancing of the peroxidase activity of Muller, because Muller is expressly teaching that Ebselen is an enhancer of the peroxidase activity and Arteel is teaching that the same Ebselen is the substrate for thioredoxin reductase.

In response to the rejections of record, Applicants note that compound claims are no longer pending whereby the anticipation rejection based upon Arteel should be withdrawn.

Regarding the obviousness rejection, as discussed with the Examiner during the above-noted interview, Applicants' specification discloses at page 2, lines 2-6, that Muller discloses that Applicants' compounds can reduce a peroxide (active oxygen) by glutathione peroxidase-like activity. However, the specification points out that the reduction of a peroxide by glutathione peroxidase is based on a totally different mechanism from that proceeded by thioredoxin reductase.

Expanding upon the above, Applicants note that Arteel is directed to the investigation of the activity of mammalian thioredoxin reductase as a peroxynitrate reductase. Arteel performs experiments with ebselen, such as disclosed at page 265, right-hand column. Moreover, Arteel discusses, at page 268, the right-hand column, an affinity of ebselen for thioredoxin reductase, and the role of thioredoxin in the thioredoxin reductase-albumin complex.

In contrast, Muller is directed to the glutathione peroxidase-like activity of ebselen in vitro, in contrast to its sulfur analog, PZ25, and to its antioxidant activity. Muller discloses glutathione peroxidase and glutathione, and does not teach or suggest any relation of this activity to thioredoxin reductase activity, thioredoxin activity and/or thioredoxin/thioredoxin reductase activity.

Moreover, glutathione is a small peptide acting non-enzymatically, and therefore requires high concentrations. It is a different mechanism than the enzymatic system of the present invention.

Applicants respectfully submit that the prior art of record does not provide any motivation for combining Arteel and Muller. In this regard, during the interview the Examiner alleged similarity between the systems disclosed by Arteel and Muller. If the Examiner deems that the prior art does provide motivation for combining the disclosures of Arteel and Muller, the Examiner is respectfully requested to provide documentary evidence to support such assertion. This would afford Applicants an opportunity to reply to the specific disclosures relied upon, and to address why one having ordinary skill in the art would not be motivated to combine the diverse disclosures.

Still further, even if for the sake of argument the disclosures of Arteel and Muller were combined, Applicants' invention would not be at hand, because a combination of the two disclosures would not motivate one having ordinary skill in the art to arrive at Applicants' recited methods.

Expanding upon the above, Applicants directed the Examiner's attention to Engman et al., "Diaryl chalcogenides as selective inhibitors of thioredoxin reductase and potential antitumor agents", Anticancer Res. 1997 Nov-Dec;17(6D):4599-605, which is being submitted with the above-noted Supplemental Information Disclosure Statement submitted on even date with this

response. From a review of this document, it can be seen that Engman as well as Arteel do not disclose the use of Ebselen as a substrate for thioredoxin reductase. Instead, Arteel pertains to Ebselen oxide created by incubation with peroxynitrite. In its results and discussion, at page 268, right column, at the top of the column, Arteel cites Engman (Reference NO. 22) for its disclosure of Ebselen being an inhibitor of thioredoxin reductase, and discuss a mechanism that in not in conformance with that of the presently disclosed and claimed invention. Furthermore, Arteel does not teach or suggest any effect of thioredoxin with ebselen. Therefore, this prior art, as stated in Engman merely discloses, "The organoselenium compound Ebselen was found to be a competitive inhibitor of human thioredoxin redcuctase (Ki 2.8 microM), while a number of organotellurium compounds were found to be noncompetitive inhibitors (Kis 2.3 and 35.2 microM).

Applicants respectfully submit that a substance which is an inhibitor of an enzyme is not a substrate unless it is a suicide substrate, which kills the enzyme by covalent modification. For example, the Abstract in Arteel merely states in the last sentence that,"In parallel experiments, thioredoxin reductase efficiently reduced ebselen selenoxide back to ebselen". Moreover, in the above-noted portion of page 268 of Arteel, it is stated that, "Ebselen has been shown previously to have an affinity for TR, competitively inhibiting the Trx-dependent reduction of insulin by TR with an apparent K_i of 2.8 μM (22)." Arteel shows no effect of thioredoxin on reduction of Ebselen selenoxide by NADPH and thioredoxin reductase.

Thus, the prior art does not teach or suggest the invention as disclosed and claimed by Applicants. Thus, amongst other deficiencies in the prior art of record, the prior art does not teach or suggest that Ebselen is an outstanding substrate for reduced thioredoxin. This is not

taught or suggested in the prior art of record and, without wishing to be bound by theory, is an important manner in which ebselen hinders inflammation by preventing thioredoxin from reducing and activating a range of transcription factors, including NFkB. Thus, Ebselen can target both thioredoxin reductase and thioredoxin with separate results.

Moreover, as noted above, prior to Applicants' invention, one having ordinary skill in the art would be under the belief that Ebselen is an inhibitor of thioredoxin reductase, and not a substrate as disclosed and claimed by Applicants.

In contrast to the prior art of record, the present invention demonstrates that Ebselen is a substrate being reduced by NADPH and thioredoxin reductase with a low Km-value meaning that it is a very good substrate undergoing unlimited cycles of oxidation reduction in the presence of hydrogen peroxide without affecting the activity of the enzyme. The reduced Ebselen is called Ebselen selenol and has the Se-N bond broken by reduction. The selenol is oxidized back to Ebselen by hydrogen peroxide or another peroxide and a new cycle starts. The reaction is ultimately driven by NADPH. Reduced thioredoxin strongly enhances the thioredoxin reductase reaction which is also proven by determination of the rate of reduction of Ebselen by reduced thioredoxin using kinetics with tryptophan fluorescence. The result, never seen before, is that ebselen is a very efficient oxidant of reduced thioredoxin.

For the reasons set forth above, the methods recited in Applicants' claims are not taught or suggested by the prior art, whereby the claims are patentable over the prior art of record, and the rejections should be withdrawn.

CONCLUSION

In view of the foregoing, the Examiner is respectfully requested to reconsider and withdraw the rejections of record, and allow each of the pending claims.

Applicants therefore respectfully request that an early indication of allowance of the application be indicated by the mailing of the Notices of Allowance and Allowability.

Should the Examiner have any questions regarding this application, the Examiner is invited to contact the undersigned at the below-listed telephone number.

Respectfully submitted,
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September 10, 2003
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